Quarterly Progress Report

N01-NS-1-2333

Restoration of Hand and Arm Function by Functional Neuromuscular Stimulation

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Contract abstract

The overall goal of this contract is to provide virtually all individuals with a cervical level spinal cord injury, regardless of injury level and extent, with the opportunity to gain additional useful function through the use of FNS and complementary surgical techniques. Specifically, we will expand our applications to include individuals with high tetraplegia (C1-C4), low tetraplegia (C7), and incomplete injuries. We will also extend and enhance the performance provided to the existing C5-C6 group by using improved electrode technology for some muscles and by combining several upper extremity functions into a single neuroprosthesis. The new technologies that we will develop and implement in this proposal are: the use of nerve cuffs for complete activation in high tetraplegia, the use of current steering in nerve cuffs, imaging-based assessment of maximum muscle forces, denervation, and volume activated by electrodes, multiple degree-of-freedom control, the use of dual implants, new neurotization surgeries for the reversal of denervation, new muscle transfer surgeries for high tetraplegia, and an improved forward dynamic model of the shoulder and elbow. During this contract period, all proposed neuroprostheses will come to fruition as clinically deployed and fully evaluated demonstrations.

Summary of activities during this reporting period

The following activities are described in this report:

- *Calculation of shoulder muscle volumes via MRI image processing*
- *Feedback control of hand position and orientation in high tetraplegia*
- *Regrowth of a paralyzed nerve through a denervating epineural sheath*
- *Subject recruitment for neuroprosthesis implementation*

Calculation of shoulder muscle volumes via MRI image processing

Contract section: E.1.a.ii.4.1 Model customization: muscle volume estimates via MRI

Background

The development of a neuroprosthetic for persons with high tetraplegia utilizes a musculoskeletal model of the shoulder. The parameters for this model are currently based on cadaver studies. Maximum muscle force is the most difficult parameter to quantify, especially for muscles with stabilizing actions, such as those located in the rotator cuff. The maximum muscle force is approximately proportional to muscle volume via the following:

$$\text{PCSA} = \frac{\text{Muscle Volume}}{\text{Muscle Fiber Length}}$$

$$\text{Maximal Force} = \text{PCSA} \cdot \text{Specific Tension}$$

The volume estimation has utilized many modalities, including ultrasound, bioelectric impedance analysis (BIA), dual-electron x-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). MRI has been viewed as the gold standard [1, 6], since it has greater resolution than ultrasound and BIA, improved soft tissue contrast over DXA and CT, and no harmful ionizing radiation, as there is with DXA and CT. Previous MR volume

estimation includes volume estimates of leg muscles (with segmentation via stereological techniques [2] or manual outlining [4, 7]), volume estimates of rotator cuff muscles [3], and complete visualization of shoulder/upper arm muscles [5] (including muscle volumes, muscle attachment points, and bony contours).

The objective of this study is to segment and calculate the individual volumes of the muscles of the shoulder and upper arm via MRI image processing.

Methods

Scan Acqusition

The equipment used was a 1.5 Tesla Siemens Sonata MR scanner, with a phased array body coil positioned over the anterior portion of the shoulder. The scan parameters were:

- TR/TE – 13 ms/7.15 ms
- Flip angle - 25°
- Field of view – 310 mm
- Voxel dimensions – 0.69 mm x 0.69 mm x 1.5 mm

The region of interest (ROI) went from the 4th cervical vertebra to the olecranon, which was chosen to include the following muscles: Biceps Brachii, Coracobrachialis, Deltoid, Infraspinatus, Levator Scapula, Pectoralis Major, Pectoralis Minor, Rhomboid Major, Rhomboid Minor, Serratus Anterior, Subclavius, Subscapularis, Supraspinatus, Teres Major, Teres Minor, Triceps Brachii, and Trapezius.

Segmentation

The software used for segmentation was Analyze (BIR, Mayo Clinic). The segmentation procedure involved determining the appropriate slice orientation for a given muscle, outlining the object (i.e. muscle) every three (3) slices, propagating the object, and manually adjusting the contours.

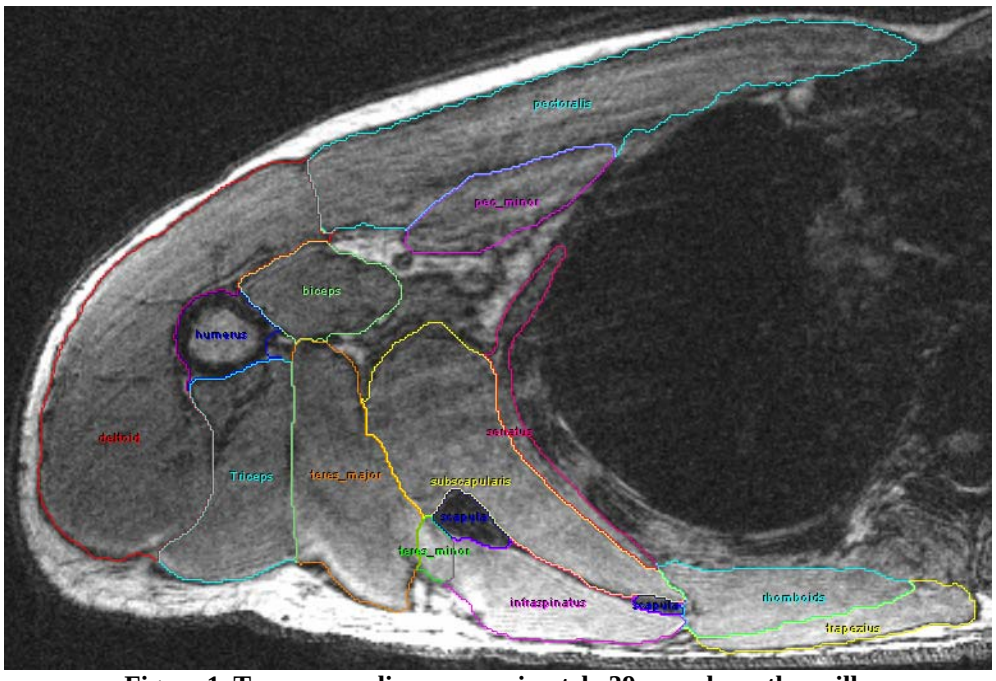


Figure 1. Transverse slice, approximately 39 mm above the axilla

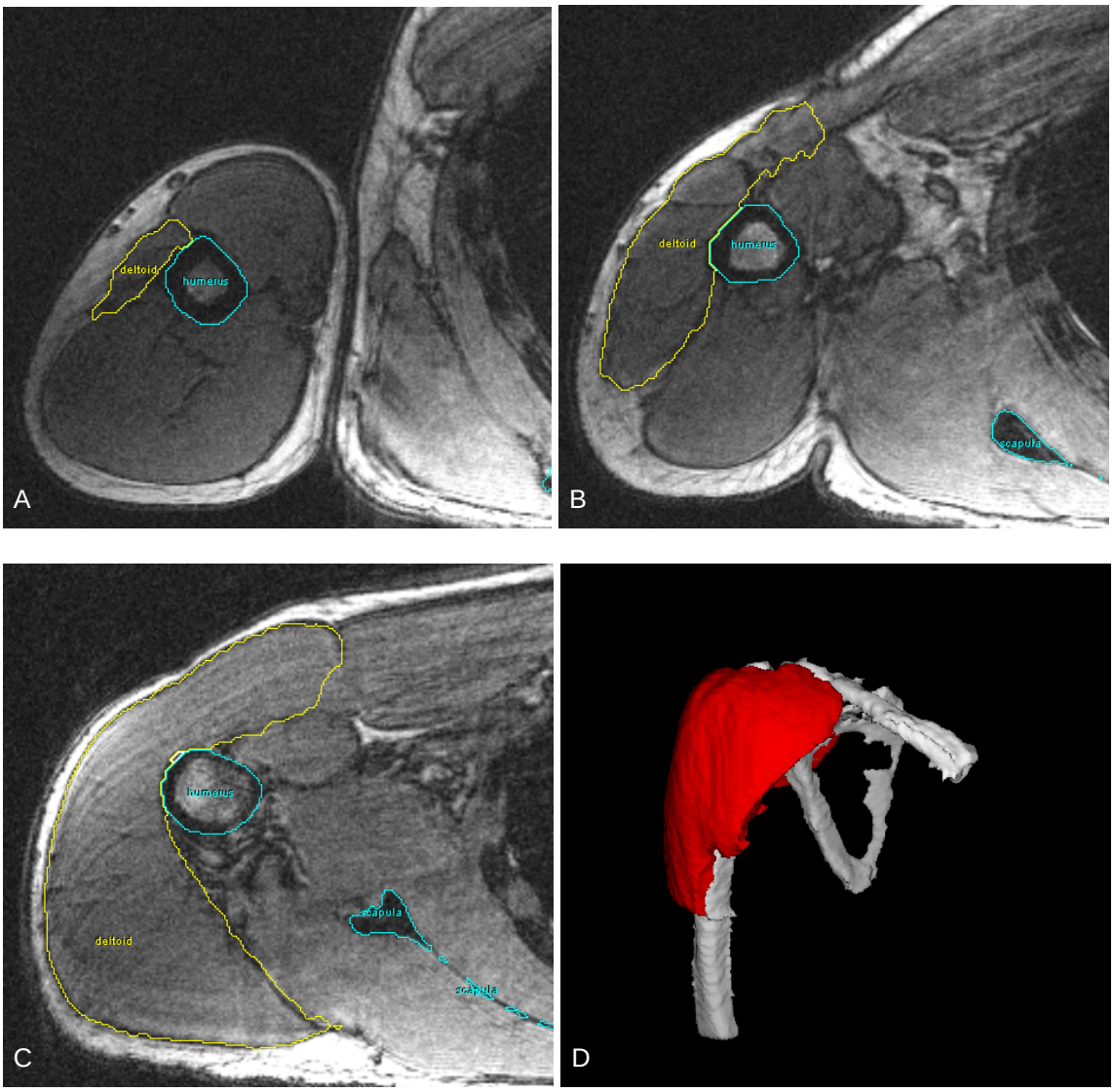


Figure 2. Segmentation of the deltoid. Figures 2A - 2C move superiorly through the muscle. Figure 2D is the surface rendering of the deltoid.

Results

The results of the volume estimates from the muscles segmentations are shown in Table 1. The Pectoralis Major could not be fully segmented due to motion artifact.

Surface renderings of the muscles are shown in Figures 3-5.

Table 1. Shoulder Muscle Volume Estimations

Muscle	*Volume (cm3)*
Biceps/Coracobrachialis	258.63
Deltoid	594.84
Infraspinatus	181.92
Pectoralis Minor	91.60
Rhomboids	120.54
Serratus Anterior	179.97
Subclavius	9.30
Subscapularis	258.86
Supraspinatus	78.46
Teres Major	180.62
Teres Minor	45.80
Triceps	563.29
Trapezius	222.44

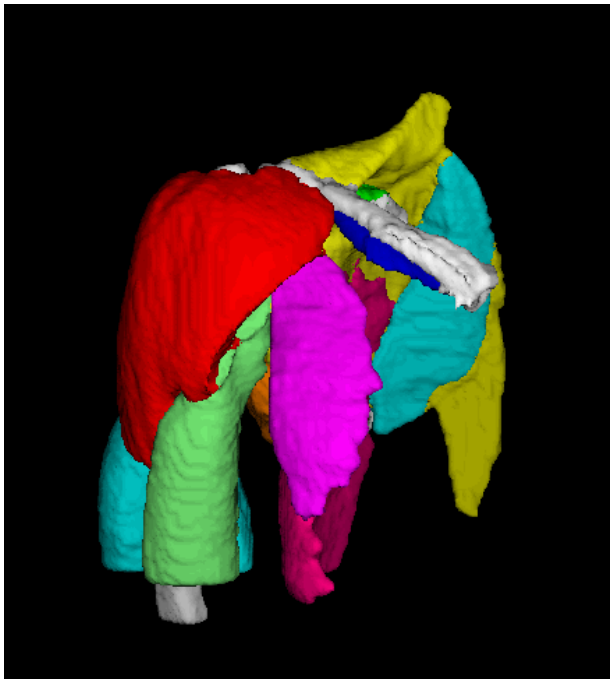


Figure 3. Anterior view of the shoulder.

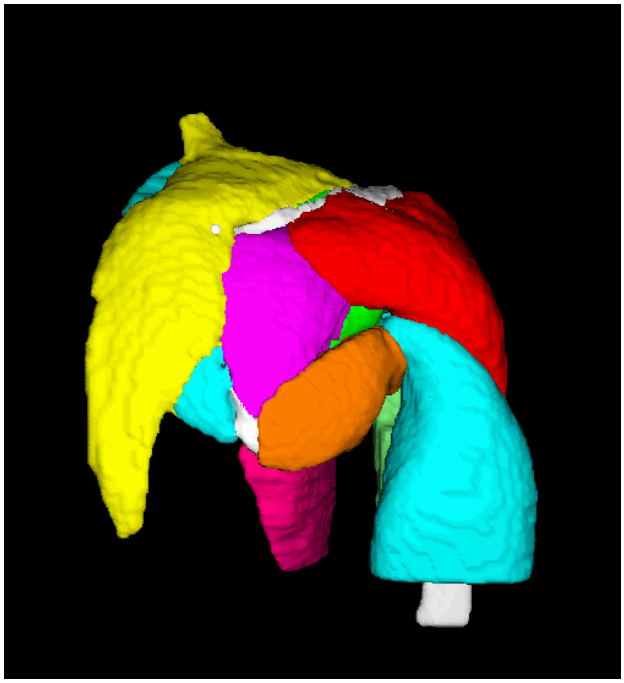
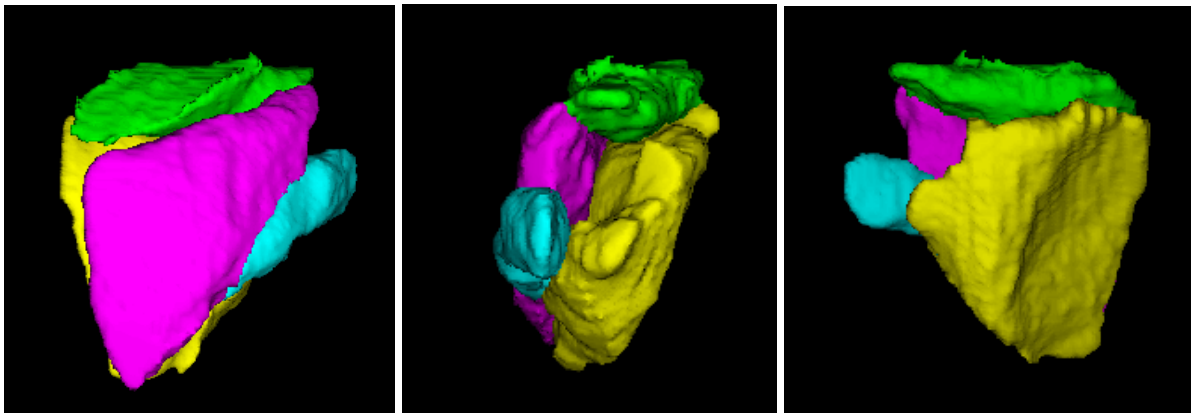


Figure 4. Posterior view of the shoulder.



a) **b)** **c)**

Figure 5. Muscles of the rotator cuff. a) posterior view, b) distal view, c) anterior view.

Discussion

Of the 17 target muscles, 13 muscle groups were successfully segmented. Due to a lack of consistent visible borders, the following groupings were made:
• Biceps Brachii & Coracobrachialis
• Rhomboid Major & Rhomboid Minor

Levator scapula could not be segmented as it originated above the upper bounds of the image set. Pectoralis major could not be segmented due to extreme motion artifact. Volumes of muscles located about the ribs (serratus anterior, pectoralis minor, subscapularis) are skewed by the presence of motion artifact, due to the subject's breathing (Figure 6).

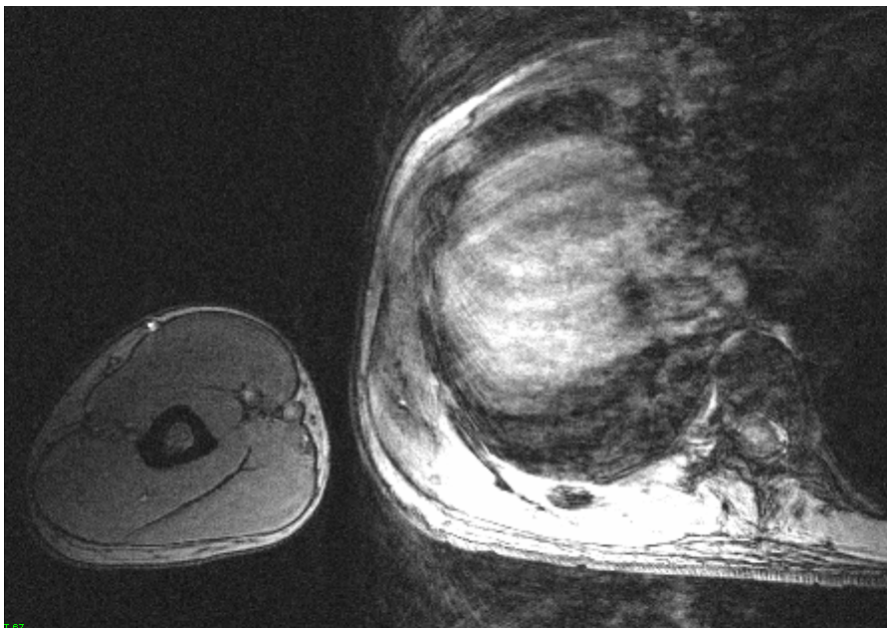


Figure 6. Example of motion artifact.

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Feedback control of hand position and orientation in high tetraplegia

Contract section: E.1.a.ii.4.3 Development of forward dynamic model of human arm

Introduction

Individuals with C3/C4 spinal cord injury lose voluntary control of almost all muscles of the upper extremity. The controller for the neuroprosthetic system needs to not only generate the appropriate levels of muscle activation, based on the user commands, but also compensate for errors caused by external disturbances and fatigue. This is necessary, because at that level of injury, voluntary correction for errors in the performance of the neuroprosthesis is not possible. In addition, due to the large number of shoulder and elbow muscles that must be controlled in high tetraplegia, purely experimental methods for developing the neuroprosthesis are inefficient and impractical. The goal of this section of the contract is to use a model-based approach to develop and test a feedback controller for this system.

Methods

The musculoskeletal model of the shoulder and elbow used in this study was described in a previous Quarterly Progress Report (QPR#9, Apr-Jun 2003). The set of muscles that need to be controlled by the system was determined using this model. The model was customized to simulate a person with C3-C4 level injury, and the paralyzed muscles that can be stimulated with cuff, epimysial and intramuscular electrodes were included. A large set of inverse simulations was run for both single joint movements (shoulder abduction/adduction, flexion/extension, horizontal flexion/extension, internal/external rotation and elbow flexion/extension and pronation/supination) and a set of functional movements comprised of activities of daily living (ADL) such as feeding, drinking, combing the hair, etc. Table 2 shows the list of muscles that are included in the system.

trapezius	levator scapulae
rhomboid	serratus anterior
deltoid	infraspinatus
latissimus dorsi	supraspinatus
biceps	pectoralis major
triceps	brachialis
anconeus	supinator
pronator quadratus	

Table 2. Muscles included in the neuroprosthetic system. The trapezius and levator scapulae are voluntary; the rest are paralyzed, and assumed to be stimulated by cuff, epimysial or intramuscular electrodes.

The open-loop controller that calculates the muscle activations required for a desired movement was designed as a static two-layer artificial neural network (ANN). It has a tangent-sigmoidal activation function for the hidden layer and a linear activation function for the output layer. It was developed using the musculoskeletal model. First, a large set of inverse simulations was performed, to obtain the activations needed for a range of postures. Then, the neural network was trained with the endpoint position and orientation as inputs, and the required activations as outputs.

In order to correct for position and orientation errors that are caused by fatigue or external disturbances, such as masses added to or removed from the hand, a feedback loop needs to be added to the previously designed controller. The relationship between error and change in muscle activation is modeled by a set of "fuzzy logic" rules. These rules use the previously developed map between endpoint position and orientation and muscle activation. On that map, the desired position corresponds to a set of muscle activations, and the actual position corresponds to a different set. The difference between these sets, as well as the distance between the desired and actual position, are the inputs to the fuzzy controller, and the output is the change in muscle activations that will move the arm toward the desired position.

Results

Figure 7 shows the predictions of the open-loop controller, which is an ANN with 20 neurons in the hidden layer, for the activation of two muscles, middle deltoid and upper trapezius, during a humeral abduction movement. The RMS error is 4.47% for the middle deltoid, and 6.05% for the upper trapezius.

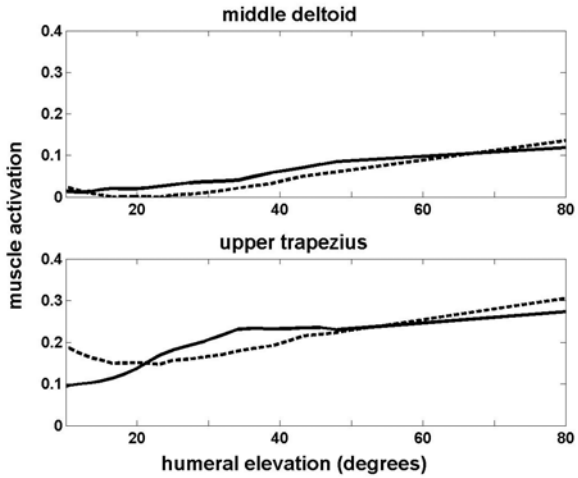

Figure 7. Open-loop controller. The solid lines are the activations calculated by the model, and the dotted lines are the ANN predictions.

The preliminary results show that the ANN can accurately predict the muscle activations needed for a desired posture, and can therefore be used as the open-loop part of the neuroprosthesis controller. The performance of the ANN can be improved by optimizing its parameters.

Also, it is demonstrated that the use of a musculoskeletal model, simulating a C3-C4 SCI individual, can facilitate both the development and the testing of the feedback controller.

Next Quarter

The performance of the overall controller will be evaluated by placing it in series with the forward model. A set of forward simulations will be performed with the output of the controller as input to the model, and the resulting endpoint position and orientation will be compared with the desired ones. Subsequently, the ability of the controller to correct for errors will be tested by using the model to simulate the effects of fatigue, different masses added or removed from the hand, and external forces representing obstacles.

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Regrowth of a Paralyzed Nerve through a Denervating Epineural Sheath

Contract section: E.1.c Re-innervation of denervated muscle for electrical activation

Abstract

This work aims to show that denervated epineural sheaths can serve as conduits for regrowth of a paralyzed nerve, and that this paralyzed nerve can then serve as a conduit for command signals from an electronic stimulation system. A rat model was created with a spinal cord injury and a transection of the tibial nerve to imitate a denervated nerve. One week later, the paralyzed peroneal nerve was transferred to the denervated stump of the tibial nerve. Three weeks after that, force analysis showed that there was significant regrowth of the peroneal nerve down the epineural sheath of the tibial nerve, and that this technique can be used to help restore motor function.

Introduction

In spinal cord injury (SCI), three types of motor neuron conditions exist. Some upper motor neurons (UMN) are intact (i.e., under voluntary control – left panel of Figure 8), some lower motor neurons (LMN) are intact but are paralyzed due to damage to the UMN (middle panel of Figure 8), and some LMN are dead because they have sustained damage to the cell body of the LMN (right panel of Figure 8). Nerves with intact LMNs are dubbed ”paralyzed nerves”, whereas those with damage to the LMN cell body are call ”denervated nerves”.

In Functional Electrical Stimulation (FES), the goal of the system is to create muscle function. The system works by stimulating a paralyzed LMN, which serves as a conduit for the stimulation signal. However, in the case where the target muscle is innervated by a muscle that is denervated due to the SCI, the nerve cannot be used to conduct the stimulation signal to the target muscle. The project at hand aims to remedy that situation by attempting to regrow a paralyzed nerve down the epineural sheath of a denervated nerve. Denervation is a general problem in SCI, so there have been other ways to try to solve the problem [6, 4, 3, 8]. However, for the muscles of the elbow and the shoulder (the main motivation behind this research), many of these techniques do not work. So, if this technique proves suitable for restoring mobility, it will help further the goal of FES in restoring muscle function.

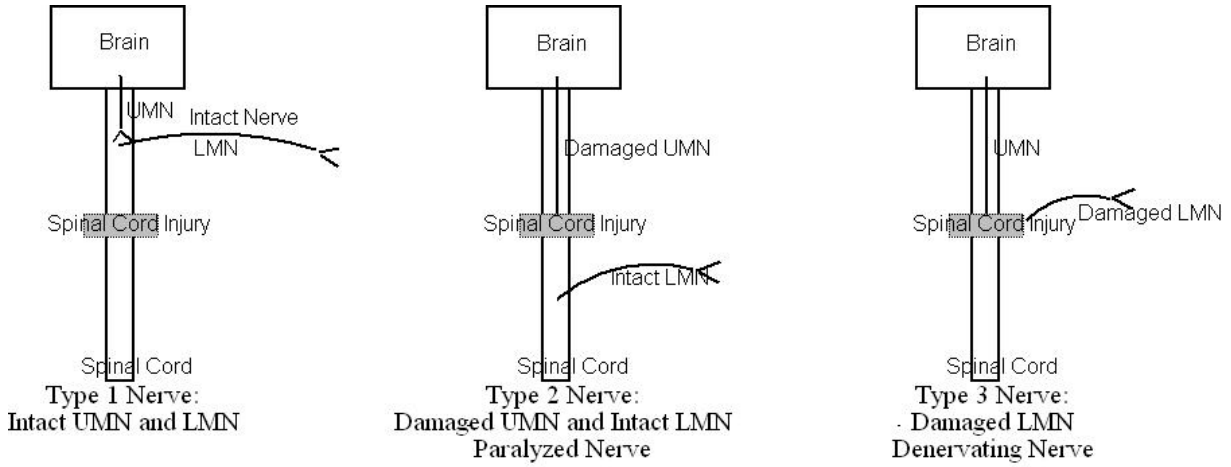

Figure 8. Illustration of the three types of nerves that can be found in a spinal cord injury patient.

Background

Injury to Peripheral Nerves

When a peripheral nerve is injured, it undergoes a process called ”Wallerian Degeneration”. This phenomena is seen regardless of the mechanism of the injury [5]. Several events are indicative of Wallerian degeneration. The axoplasm undergoes disruption, fragmentation of neural tubules and neurofilaments leads to a loss of longitudinal orientation, the mitochondria become swollen, discontinuities develop in the axolemma, and proliferating Schwann cells and macrophages further degrade the axon [5]. Since these symptoms are seen regardless of the mechanism of the injury, a transected peripheral nerve can model denervation due to damage to cell bodies in the spinal cord.

Current Techniques

Currently, there are three major methods for treating denervation in SCI patients. Each of these will be discussed in some detail in the following sections.

Tendon Transfers

The first technique to create muscle function when a muscle becomes denervated is not neurological, but muscular. When there are multiple muscles, some of which are denervated, that are similarly oriented and elicit similar movements, a tendon transfer can be performed to make the non-denervated muscle perform the function of the denervated one [3]. The tendon of the non-denervated muscle is removed from its normal insertion and attached to the tendon of the denervated muscle, such that the non-denervated muscle performs the function of the denervated muscle. This can be done with the donor muscle being either a muscle still under voluntary control, or with one that is paralyzed but can be stimulated with techniques such as FES, but is historically performed with voluntary muscles [3]. However, in the shoulder, where the muscles fan out and attach in many places, there are no good donor muscles that can be used with this technique.

Peripheral Nerve Rerouting

Conceptually analogous to the tendon transfer, except with nerves, this technique involves transferring a nerve that is under voluntary control, and therefore has its roots above the SCI, to a denervated nerve [8]. The patient then needs to be retrained to use the nerve to control its new destination muscle. Although this technique is somewhat successful, it is not optimal for a couple of reasons. First, again, there is a lack of donors in the shoulder and elbow of individuals with high cervical spinal cord injury. Second, even if a donor was available, it is usually not worth the loss of already restricted movement for the partial restoration of a different motion.

Direct Muscle Neurotization

The final major technique for addressing the problem of denervation is Direct Muscle Neurotization, which involves removing an entire neuromuscular junction from a donor and implanting it into a recipient muscle [6]. Although this can be done, through an end-to-side anastomosis to a neighboring nerve, with relatively little damage to existing nerves, the extensive branching that is found in the nerves of the shoulder, on top of the complexity of the surgical procedure, makes this an impractical option.

Related Experiments

It has been shown [2] that it is feasible for a nerve to regrow down an empty epineural sheath. It was shown that that an active nerve would regrow to the same extent if an empty epineural sheath was used, as opposed to a section of nerve that is immediately transferred from somewhere else [2]. Therefore, we know that it is possible for a healthy nerve to regrow down a path left by a denervated nerve.

An earlier study [7] showed that in baboons, blocking the conduction of signals through a nerve had no effect on its ability to regenerate after a crush injury. In this experiment, a tourniquet around the knee was used to simulate an upstream lesion. However, this simulation is clearly not the same as a SCI, although the experiment does show that a nerve can regrow even when no signals are conducted through it.

A similar experiment was performed in human subjects where the paralyzed intercostal nerve was transferred to a denervated phrenic nerve, to be used with a diaphragmatic pacemaker [4]. The results showed that the regrowth occurred to the extent where the patient could survive with just the pacemaker and no external pressurize ventilators. However, the study does not mention a quantitative measurement of the extent of the regeneration, which must be known before it becomes feasible in shoulder and elbow muscles.

Methods and Materials

Testing of the hypothesis that has been put forth in this document requires a multi-stage procedure, first to induce the injury, then to perform the graft, and finally to test the regeneration. An animal model was created to explore this phenomena.

Any mammal would be sufficient for this study, since Wallerian degeneration is the same in all species [5]. Rats were chosen for the model because they have nerves that are large enough to manipulate and transfer, and are also relatively inexpensive. Based on previous studies, approximately 6-12 successful trials are expected to be required to find statistical significance in the results gathered from these experiments.

SCI and Denervation

The first of the two survival surgeries was used to create the SCI and to create the denervation model. Under an anesthetic mixture of Ketamine, Xylazine and Acepromazine, the spinal cord was exposed at around T7-T11 through a laminectomy, as shown in Figure 9. Using the controlled crush developed at Acorda Therapeutics [1], the spinal cord was crushed for 30 seconds. Since it can be difficult to exactly control the area of a spinal cord lesion, the denervating nerve was not modeled as shown in Figure 8. Instead, the left tibial nerve was exposed, as shown in Figure 10 and was transected. The proximal portion was buried into a neighboring muscle, while the distal portion was left to denervate. A summary of the first procedure can be seen in Figure 11.

Nerve Transfer

One week after the first procedure, the leg lesion site was reopened under the same cocktail anesthesia. The peroneal nerve was transected. The proximal portion of the peroneal nerve, which models the paralyzed nerve, was sutured to the distal portion of the tibial nerve, which models the denervated nerve. A summary of this second procedure can be seen in Figure 12.

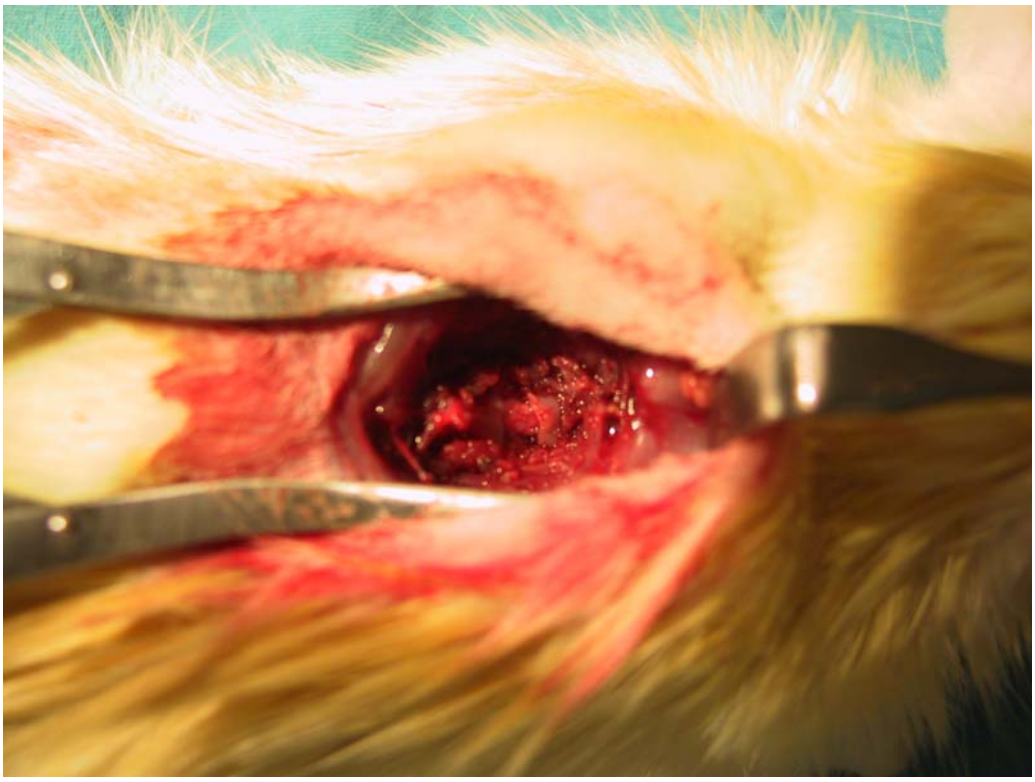

Figure 9. Spinal cord is exposed, about to be crushed.

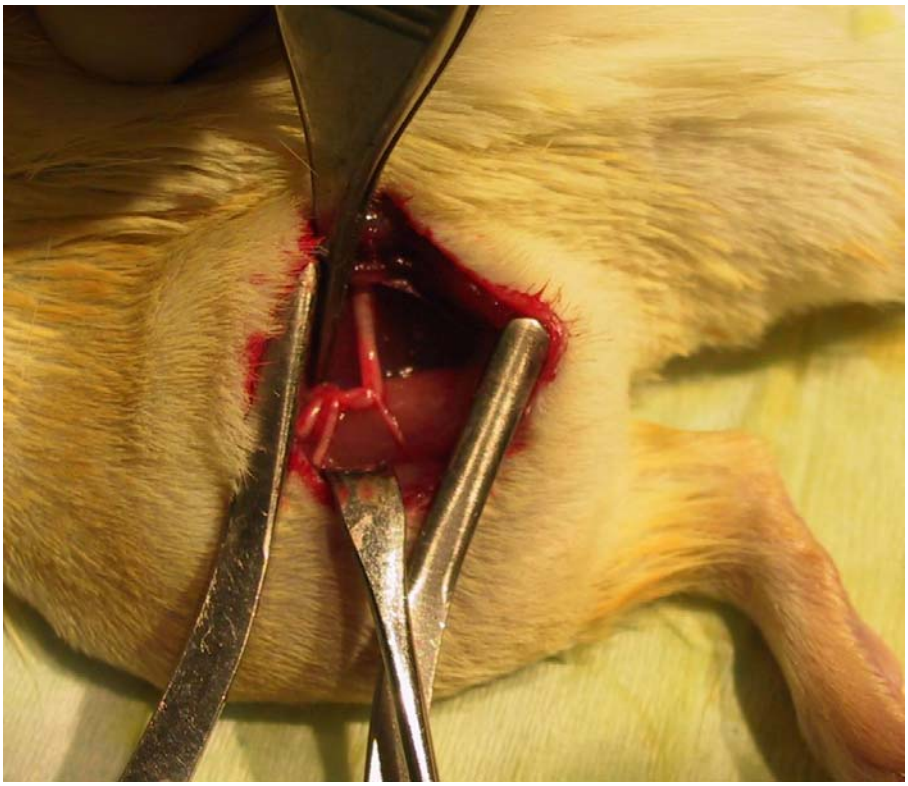

Figure 10. Sciatic junction is exposed - both the tibial and peroneal nerves can be seen.

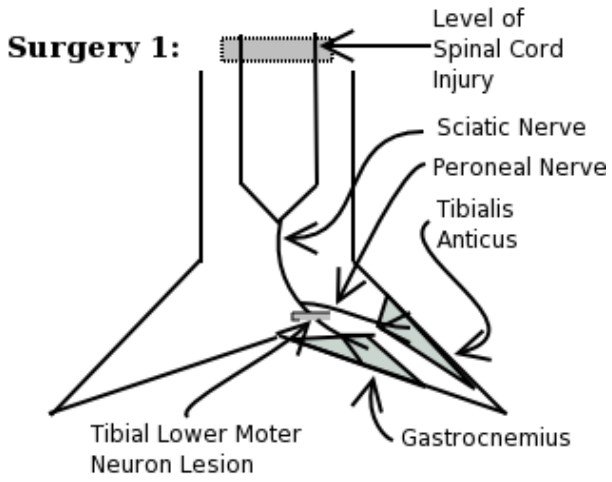

Figure 11. Diagram of the first surgical procedure - gray boxes represent lesions.

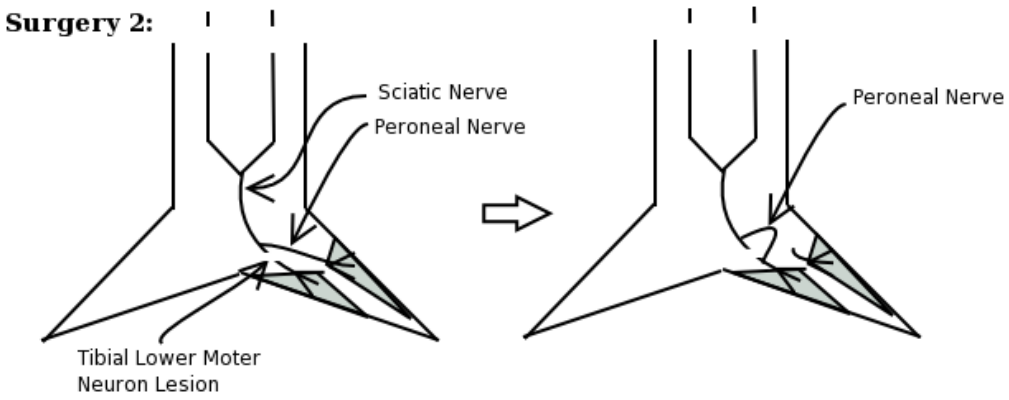

Figure 12. Diagram of the second surgical procedure - Transfer of peroneal nerve to the denervated stump of the tibial nerve.

Force Analysis and Histology

The final surgery was a non-survival data-collection procedure. The gastrocnemius, to which the tibial nerve leads, was exposed in its entirety and was attached to a force transducer (ELFS-T3E-50N-/R) manufactured by Entran. After taking a length-tension curve, the peroneal nerve was stimulated above the transfer site, such that the stimulation would travel initially down the peroneal nerve, through the reinnervated tibial nerve, and then to the target muscle, the gastrocnemius. The force generated by the gastrocnemius was measured with various pulse widths and amplitudes, as well as under tetani. The proximal tibial nerve (which had been previously disconnected from the gastrocnemius) was stimulated to demonstrate that no force was produced, i.e., that all reinnervation was through the donor nerve. To form a basis for comparison, the same procedure was performed on the right side, making sure to pull the muscle to the same point on the length-tension curve. This allowed the experiment to be controlled for muscle atrophy due to the SCI, and physiological differences between individual rats. Finally, the spinal cord was once again exposed to ensure that the lesion was complete. The entire nerve and muscle were removed for histology. An H & E stain was performed to count the axons, a

Toliden Blue stain was performed to check for myelin, and an S100 stain was performed to check for Schwann cells.

Results

This project is just underway, so only limited results are available. One animal has survived all of the procedures and it has yielded some promising data. We found that the peroneal nerve did in fact regrow down the tibial epineural tube, and was able to produce a force that was about 50% of the force produced on the opposite side. Since complete regeneration has never been found, and since most other procedures yield a force restoration of about 30-50%, our data looks promising indeed. The tibial nerve lesion proved to be complete, as stimulation of the nerve yielded no force in the gastrocnemius. The SCI was pronounced to be complete by inspection. The results of the histology have not yet been received.

Discussion

The purpose of this experiment was to see if it was feasible to use a paralyzed nerve in conjunction with FES to address the prevalent problem of motor neuron denervation in spinal cord injury (SCI). From the preliminary results that we have gathered, we have found that the technique appears promising.

After further experimentation, if this technique proves to be feasible in the restoration of motor neuron functionality, it would provide a benefit to those patients with high level cervical SCI, who are unable to currently receive assistance from an FES system. Before the technique is developed to that stage, however, further testing is needed both in animals that more closely mimic human conditions and in humans.

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Subject recruitment for neuroprosthesis implementation

Contract sections: E.1.a.vi.4.3 Implementation of neuroprostheses for high tetraplegia
E.2.a.ii.4.3 Implementation of advanced upper extremity neuroprosthesis

Summary

A significant effort has been made over the past few quarters to identify individuals with cervical level spinal cord injuries who would be appropriate candidates to receive the FES systems that have been developed under this Contract. Individuals with SCI at the C1-C4 levels are candidates for the "high tetraplegia" neuroprosthesis, while individuals with SCI at the C5-C6 level are candidates for the "improved C5-C6" neuroprosthesis. Research protocols have been approved by both NIH's and local Institutional Review Boards (IRBs). Potential candidates have been referred to our center by physicians or other clinicians, or contacted us requesting further information. Individuals who are interested in being considered for these neuroprostheses are invited to our center for an evaluation. This evaluation is needed to see whether the necessary muscles can be electrically activated, and to determine if there are other health problems that would be contraindications for the neuroprostheses.

There are currently two individuals who have been identified as appropriate candidates for the high tetraplegia neuroprosthesis. A final evaluation needs to be done before the candidate will be selected. Four individuals have been identified as appropriate candidates for the improved C5-C6 neuroprosthesis, although two of the candidates seem more motivated than the others. As with the high tetraplegia candidates, a final evaluation will be performed before the candidate is selected.

As the candidates have been evaluated, the details of the surgical procedures have been reviewed and finalized. In addition, the necessary implant components and surgical equipment are been assembled. It is believed that the implantation of nerve cuff electrodes will occur in two subjects (one with C1-C4 level SCI and one with C5-C6 level SCI) in the next quarter.